UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,586	04/23/2001	Kenji Kadomatsu	SPO-113	7871

23557 7590 06/03/2003

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	16

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Appli ation No. 09/763,586	Applicant(s) KADOMATSU ET AL.	
	Examin r J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5 and 7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11, 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's election without traverse of Group I, claims 1-4 and 6 in Paper No. 15, entered March 25, 2003 is acknowledged.

Claims 7-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15, entered March 25, 2003.

Information Disclosure Statement

Some of applicants' references submitted as part of the IDS have not been considered. Translations have been provided for the following references, but the translation quality prevents their being considered: JP-8-27021-A, IP 8-73498 A, WO 99/16463 A1. Translations were provided for the abstracts of the following, but not for the entire document: JP 07 009641A, and WO 99/38971 A. None of the above documents have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 recites "the method of claim 5". However, claim 5 is a non-elected claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of suppressing the activity or production of midkine, does not reasonably provide enablement for *in vivo* suppression of the activity or production of midkine in whole animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above listed claims is drawn to pharmaceutical compositions for the prevention or treatment of angiostenosis comprising a compound that inhibits the function of midkine, wherein said composition comprises an antisense oligonucleotide or an antibody targeted to midkine. The specification teaches a method of preparing a mouse model system to studying restenosis, a method for detecting midkine in said mouse model, wherein said mouse model may also utilize midkine knockout mice.

Applicants recitation of the term "pharmaceutical" in the claim language directly implicates the use of said compounds *in vivo*, since Steadman's medical dictionary broadly defines a pharmaceutical use as that which emphasizes a therapeutic use of drugs. However, the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using the compounds in *in vivo* environments.

Additionally, a person skilled in the art would recognize that predicting the successful treatment of disease using an antibody or antisense compound *in vivo* based solely on prophetic guidance is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of treating angiostenosis *in vivo*, such a disclosure would not be considered enabling since the state of antibody- and antisense-mediated gene inhibition is highly unpredictable.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification broadly claims to provide for treatment of angiostenosis. The specification does not disclose any working examples of said treatment, and otherwise supplies only prophetic guidance for direction. In light of the lack of clear guidance from the specification for how to treat angiostenosis, determination of enablement depends heavily upon the state of the prior art for support. However, as described below, the state of the art of treating any disease by successfully using the antibody- and antisense-mediated therapies as prophetically disclosed is highly unpredictable.

The following references are cited herein to illustrate the state of the art of antibody- and antisense-mediated treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the antisense therapy art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including

primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the

antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

In regards to antibody therapies, McCune et al. lists a number of side effects and notes a relatively small number of antibodies (10), all non-human antibodies, which have been FDA approved for treatment of any disease. McCune states that maximal efficacy is observed where the antigen occurs only on target cells, and that antibody binding should preferentially not reduce the level of antigen expressed. McCune goes on to note that common reactions are fevers, rigors, respiratory distress, hypotension, and severe suppression of the immune system which negatively impacts the ability to fight infections. The immune problems discussed by McCune are compounded by the understanding that nearly all antibodies used in such applications are non-human, which often illicits a cross-species reaction responsible for some of these problems. While this reference also discusses some successful cases of monoclonal antibody treatment of disease, the larger picture is that the use of antibodies as compounds for therapy requires a large amount of trial and error experimentation, and that success is highly unpredictable.

Thus, both the instant specification and the prior art fail to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of treating disease using the instantly claimed compounds, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the preparation of a mouse model to study angiostenosis as being correlative or representative of the successful *in vivo* use of antisense or antibody compounds in the treatment of angiostenosis suspected of being associated with midkine expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with

the efficacy of antibody- or antisense-mediated treatment or prevention of any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by such compounds.

The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered, and most importantly, that the midkine target is sufficiently inhibited such that treatment and/or preventive effects are provided for *in vivo*. Since the specification fails to provide any guidance for the successful treatment of angiostenotic conditions, and since resolution of the various complications in regards to targeting a particular target in an organism is highly unpredictable as outlined above, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et al. (Teratology 1997, 55:213-223).

The invention of the above listed claims is drawn to a pharmaceutical composition for the prevention or treatment or treatment of angiostenosis, comprising a compound inhibiting the function of midkine, wherein said inhibitor may be an antisense oligo that is directed against midkine, or said compound that results from a screening method for inhibitors of midkine.

Griffith et al. teaches an antisense oligo in saline solution that is directed to and inhibits the expression of midkine.

Accordingly, this reference teaches all the structural limitations of the above claims. While this reference does not teach the functional limitations of preventing angiostenosis, such functional language, because such language is considered to constitute an intended use, and therefore does not carry patentable weight. As per M.P.E.P. 2111.02:

> If the body of a claim fully and intrinsically sets forth all of the limitations the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. ...If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim.

Also as per M.P.E.P. 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established.

Therefore, since the above reference teaches all the structural limitations of the instantly claimed compositions, said compound is also considered capable of performing the functions claimed by applicant, rendering the instant claims anticipated.

The above claims have also been rejected for lacking enablement in regards to a pharmaceutical use, because the language pertaining to intended use must be considered under 35 U.S.C. § 112 1st paragraph enablement. However, such language is not given patentable

consideration in the analysis of anticipation or obviousness for reasons given above. Therefore, because the enablement rejection is directed to the intended use aspect of the claims, and not the compounds per se, the instant art rejection is considered appropriate because it is directed exclusively to the compounds themselves.

Furthermore, although claim 6 is drawn to the compound that results from a screening process for identifying inhibitors of midkine, the patentability of a product does not depend on its method of production. If the product of the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different product. See M.P.E.P. § 2113. Therefore, Griffith et al. anticipates the product-by-process of claim 6.

Claims 1, 3, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Muramatsu et al. (Develop. Biol. 1993, 159:392-402).

The invention of the above listed claims is drawn to a pharmaceutical composition for the prevention or treatment or treatment of angiostenosis, comprising a compound inhibiting the function of midkine, wherein said inhibitor is an antibody or fragment thereof that is directed against midkine, or said compound that results from a screening method for inhibitors of midkine.

Muramatsu et al. teach an antibody in saline solution that is directed to and inhibits midkine.

For the same reasons given above, the pharmaceutical recitation of the instant claims is not given patentable consideration in the analysis of anticipation or obviousness. Therefore, the

instant art rejection is considered appropriate because it is directed exclusively to the compounds themselves.

Although Muramatsu et al. does not teach the functional limitations of preventing angiostenosis, for the same reasons as given above, such intended use language is not considered to carry patentable weight. Accordingly, Muramatsu also anticipates the product by process of claim 6 for the reasons given above. See M.P.E.P. § 2113.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
June 1, 2003

KAREN LACOURCIERE
PATENT EXAMINER